

Urinary Iodine Metabolomics as a Novel Tool for Understanding Environmentally Induced Thyroid Hormone Metabolic Alteration

Qianqian Chai, Yan Lin,* Yifang Zhu,* Jinming Liu, Xiaodi Shi, Xing Jiang, Xinchun Lu, Lailai Yan, Junfeng Zhang, Tong Zhu, Jesus A. Araujo, and Xinghua Qiu*



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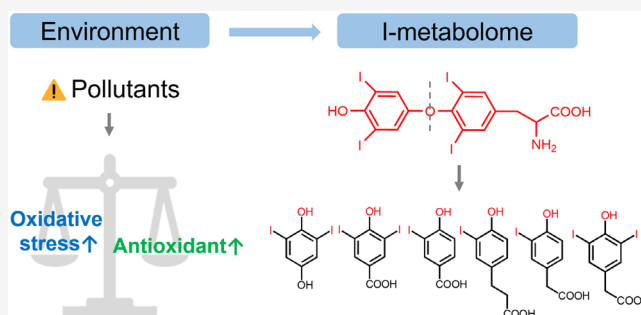
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ABSTRACT: In this study, we developed a novel iodine metabolomic method and identified 42 iodine-containing compounds in urine. Using *in vitro* experiments, we confirmed that these compounds were degradation metabolites of thyroid hormones (THs) and may be used to understand the peripheral metabolism of THs. These metabolites were then measured in urine samples collected in a natural experiment in 26 healthy adults experiencing substantial environmental changes after traveling from Los Angeles to Beijing. Despite the absence of significant alterations in iodine intakes or circulating TH levels, the level of urinary TH metabolites significantly decreased by $\leq 52.4\%$ in Beijing, in association with exposure to polycyclic aromatic hydrocarbons and metals and the subsequent oxidative–antioxidative responses. All of these changes were reversed after the participants had returned to Los Angeles. These results support the promising use of iodine metabolomics to detect early TH metabolic alteration and shed light on novel mechanisms for environmental impacts on TH homeostasis.

KEYWORDS: organoiodine metabolomics, thyroid hormone metabolism markers, natural experiment, pollutants, oxidative–antioxidative response



INTRODUCTION

Thyroid hormones (THs) belong to a group of iodine-containing organic compounds that regulate metabolism and maintain physiological function.^{1,2} Subclinical hyperthyroidism and hypothyroidism are common in populations across all age groups, and both are associated with increased risks for the development of many major illnesses such as cardiovascular diseases.^{3,4} TH homeostasis in the systemic circulation relies on balanced TH synthesis/secretion and degradation. Unlike the well-established thyrotropic feedback control of TH synthesis and release by the hypothalamus–pituitary–thyroid (HPT) axis,⁵ TH regulation via diverse degradation is less understood, despite high daily turnover rates of 10% for thyroxine (T4) and 60% for triiodothyronine (T3),⁶ and emerging evidence that metabolic changes affect TH homeostasis.⁷ Peripheral metabolism affects the speciation and activity of THs (e.g., deiodination of T4 generates more biologically active T3),⁸ as well as their physiological functions (e.g., tetraiodothyroacetic acid, a deaminated metabolite, can inhibit the pro-angiogenic effects of T4 and T3).⁹

Increasing numbers of environmental chemicals have been suggested as thyroid disruptors.¹⁰ Animal studies with large doses of exposure have revealed significant changes in circulating TH levels partially via interference with the HPT axis and iodine-centered peripheral metabolism.^{11–13} Epide-

miological studies have also shown associations between environmental factors (e.g., air pollution) and changes in the HPT axis.¹⁴ These results require a better understanding of the environmental etiology of TH dysfunction to inform preventive strategies. Unfortunately, there is no human evidence to date on which and how far pollutants would disturb peripheral TH metabolism beyond deiodination, largely due to the lack of sensitive markers to indicate metabolic variations.

In this study, we developed a non-targeted metabolomic approach to identify new organoiodine compounds in urine as hypothetical markers of TH metabolism. Combining exposure markers of key pollutants and existing data regarding biological pathways, we aimed (1) to determine whether and the extent to which drastic environmental changes would influence the levels of urinary TH metabolites, (2) to identify key exposures that could affect TH metabolism, and (3) to explore the

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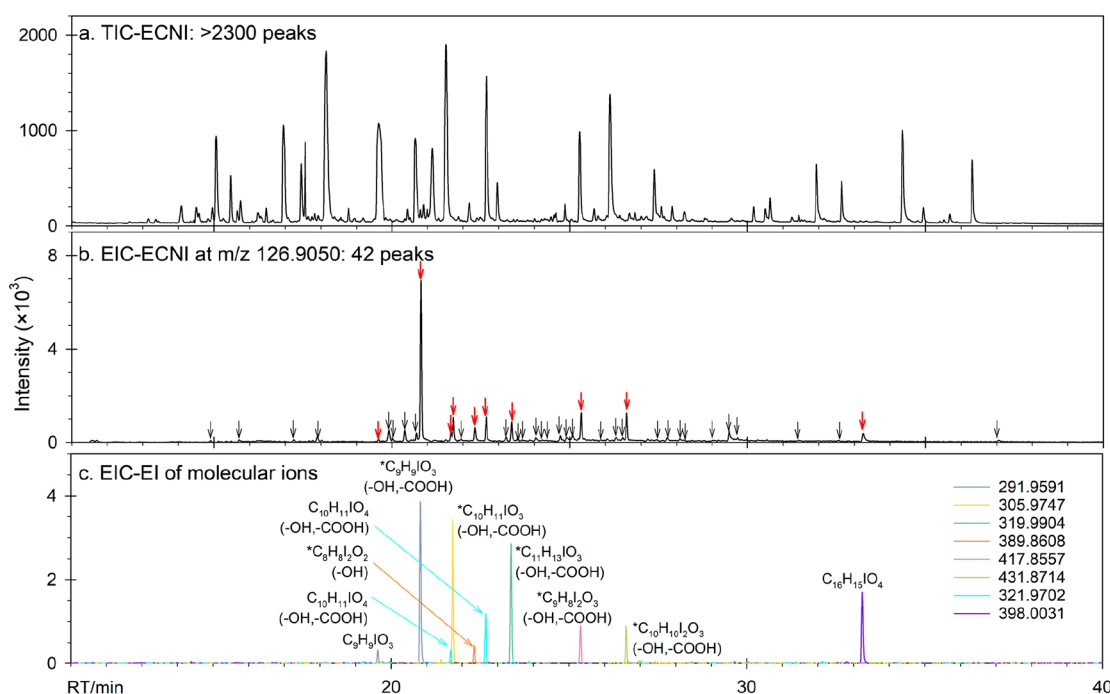


Figure 1. Chromatograms of the pooled urine sample. (a) Total ion chromatogram (TIC) of the ECNI. (b) Extracted ion chromatogram (EIC) of peaks at m/z 126.9050. (c) Peaks of the molecular ions of 10 identified iodine-containing compounds in a quality control sample after methylation. Arrows in panel b indicate detectable peaks of iodine-containing compounds, and the red arrows point to the 10 identified compounds. An asterisk before the molecular formula in panel c indicates a species confirmed with reference standards; formulas in parentheses are functional groups other than iodine.

potential mechanism linking environmental factors to TH metabolism.

METHODS AND MATERIALS

Study Design and Participants. This study was built upon a natural experiment involving healthy international travelers.^{15,16} Briefly, 26 nonsmoking university students from the University of California, Los Angeles (UCLA), were recruited and visited Peking University (PKU), Beijing, in the summers of 2014 and 2015 for 10 weeks. One to five fasting morning urine samples and one peripheral serum sample from each participant were collected in each phase, i.e., in Los Angeles (LA) before the travel (LA-before), in Beijing (BJ), and after returning to LA (LA-after). Urine samples and serum samples were stored in refrigerator at -30 and -80 °C, respectively, and protected from light. In total, 179 urine and 72 serum samples were analyzed. This study was approved by the institutional review boards of both UCLA (IRB#12000699) and PKU (IRB00001052-14037), and informed consent was obtained from each participant.

Organoiodine Metabolomics. A 2 mL aliquot of urine was spiked with deuterium-labeled surrogate standards and adjusted to pH 5.5 for the hydrolysis of conjunct compounds by β -glucuronidase-sulfatase. After the pH was adjusted to <1 , analytes were extracted with a 1:1 (v/v) hexane/methyl *tert*-butyl ether mixture, and hydroxyl and carboxyl groups were methylated with fresh diazomethane. After purification by silica gel column chromatography, deuterium-labeled internal standards (i.e., 1-nitronaphthalene and 9-nitroanthracene) were spiked for instrumental analysis. Thirteen pooled samples mixed from all urine and 12 blank samples with deionized water as the matrix were also prepared.

An Agilent (Santa Clara, CA) model 7890B-7200 gas chromatograph-time-of-flight mass spectrometer (GC-ToF-MS) was used for metabolomic analyses. A 1 μ L sample was injected at 250 °C. Two linked 15 m Rxi-5Sil columns (0.25 mm inside diameter, 0.25 μ m thickness; Restek Inc., Bellefonte, PA) were used for separation with constant helium flow rates of 1 and 1.2 mL min⁻¹ for the first and second column, respectively. The oven temperature was held at 70 °C for 1 min, increased at a rate of 6 °C min⁻¹ to 300 °C, and held for 1 min. The ToF-MS was operated in high-resolution mode with mass-to-charge ratios (m/z) of 20–500 for electron capture negative ionization (ECNI) and 34–600 for electron impact (EI) sources.

To confirm the identified iodine-containing compounds, reference standards of 3-iodo-4-hydroxybenzoic acid (I-HBA) and 3,5-diiodo-4-hydroxybenzoic acid (I₂-HBA) were purchased from Bidepharm (Shanghai, China); 2,6-diiodohydroquinone (I₂-HQ), 3-iodo-4-hydroxyphenylacetic acid (I-HPA), 3,5-diiodo-4-hydroxyphenylacetic acid (I₂-HPA), and 3-(4-hydroxy-3-iodophenyl)propionic acid (I-HPPA) were synthesized and verified by the GC-ToF-MS (EI) and ¹H and ¹³C NMR. Further details are provided in the [Supporting Information, Table S1, and Figures S1–S5](#).

Accessorial Measurements and Data. *In vitro* metabolism experiments with T4 as the substrate and horseradish peroxidase (HRP) as the catalyst were performed. T4, T3, diiodotyrosine (DIT), and moniodotyrosine (MIT) were measured in serum by high-performance liquid chromatography-triple quadrupole mass spectrometry (HPLC-QQQ-MS/MS). Concentrations of 22 elements in urine were analyzed using inductively coupled plasma-mass spectrometry (ICP-MS). Details for these experiments and measurements are available in the [Supporting Information and Table S2](#).

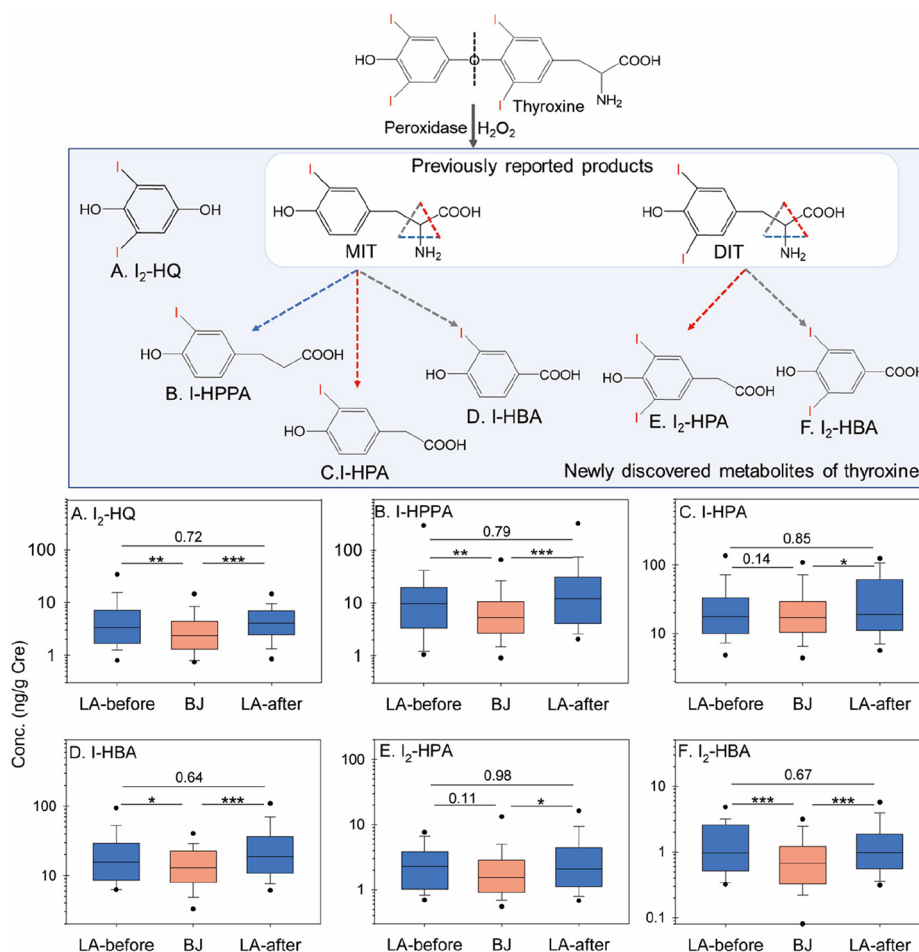


Figure 2. Proposed cleavage of the diphenyl ether link of thyroxine (top) and concentrations of confirmed TH metabolites in urine before, during, and after traveling from LA to Beijing (bottom panels A–F). Solid horizontal lines represent the median. A box represents the 25th–75th percentiles, and whiskers represent the 10th and 90th percentiles. Horizontal lines between the boxes represent the comparison of metabolite levels at different stages of travel. The numbers represent the exact *p* values, while one, two, and three asterisks indicate *p* values of <0.05, <0.01, and <0.001, respectively.

From previous studies, we obtained the exposure marker levels of urinary bisphenol A (BPA), second-hand smoke (cotinine), and polycyclic aromatic hydrocarbons (OH-PAHs); oxidative–antioxidative markers of urinary 8-isoprostane, malondialdehyde (MDA), and uric acid; and circulating 8-isoprostane, uric acid, and thyrotropin-releasing hormone (TRH).^{15–18} For these markers, each type was measured in the same batch for all samples. All urinary data were normalized according to the creatinine levels.

Statistical Analyses. The data were examined for normality and log-transformed as appropriate. Samples with no detectable target compounds were assigned to half of the limit of quantification. Given the characteristics of the panel study with multiple follow-ups for the same subject, linear mixed-effect models (LMEs) with a random intercept for the participants were primarily used in this study. To compare the overall impact of environmental factors on TH metabolites and individual exposure change during the travel, LMEs with the phase or city as an independent variable were used.

For TH metabolites and exposure estimates that significantly changed during the travel, we conducted mediation analyses to explore to the extent to which individual exposure markers explained the between-city difference in TH metabolites. This did not imply a causal mediation effect because only one

mediator was included in the analysis at a time. Instead, it was regarded as an indicator of the relative importance of individual exposures in contributing to environmentally associated changes in TH metabolites.

To examine associations between TH metabolites and urinary oxidative biomarkers, LME models with random intercepts for both the participant and city were applied. Unless stated otherwise, all models were adjusted for age, sex, and body mass index. Sensitivity analysis was conducted with additional covariates of food-related factors to evaluate the robustness of the results (details in the [Supporting Information](#)). Analyses were conducted with the “lmerTest”, “lme4”, and “mediation” packages in R software (version 4.1.1). Upon comparison of differences between cities or phases, two-tailed *p* values of <0.05 were considered statistically significant. A false discovery rate (FDR) adjustment was used in the mediation analysis, and only FDR-adjusted *p* values of <0.05 were considered statistically significant.

RESULTS

Detection of Iodine-Containing Compounds in Urine.

To identify iodine-containing compounds from the complicated matrix of urine, we developed an organoiodine

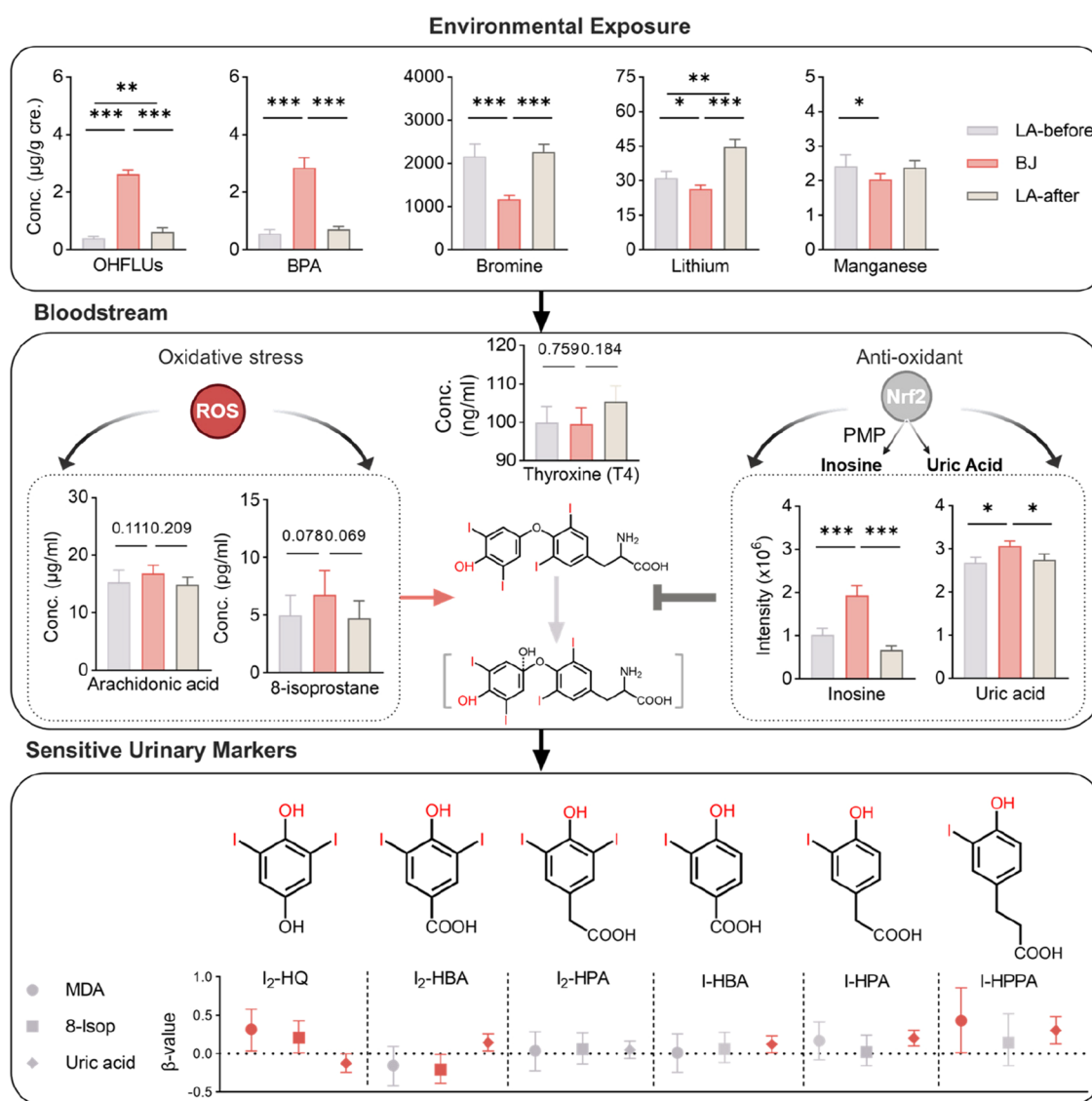


Figure 3. Proposed mechanism of environmental factors influencing TH metabolism. Abbreviations: PMP, purine metabolism pathway; MDA, malondialdehyde; 8-Isop, 8-isoprostane. Nrf2 activation is the suggested mechanistic pathway,¹⁶ colored gray.

metabolomic approach that uses a unique electron capture negative ionization (ECNI) technique to release iodine in the form of I^- , considering its high electrophilicity (electron affinity energy of 3.059 eV)¹⁹ but fragile iodine–carbon bond (dissociation energy of 2.385 eV).²⁰ Then, we took advantage of the high resolution of the ToF-MS by extracting the mass-to-charge ratio (m/z) at 126.9050 with a marked mass defect to identify iodine-containing compounds. As a result, we tagged 42 targets according to retention time from >2300 chromatographic peaks in the pooled urine sample (Figure 1 and Table S3).

Subsequently, we acquired molecular ions of tagged species using the same instrument, switching to an electron impact (EI) source. On the basis of the accurate m/z , the formulas of 10 major peaks were determined. These compounds had a double bond equivalent of 4, 5, or 9, suggesting basic phenyl ring structures (Table S4). We also found debris ions of $[M - 15.0235]^+$, $[M - 31.0184]^+$, and $[M - 59.0133]^+$, which were assigned to the neutral loss of $\bullet CH_3$, $\bullet OCH_3$, and $\bullet COOCH_3$, respectively; these findings suggested the presence of phenolic and carboxylic groups before methylation. Using laboratory-

synthesized or commercial standards, we confirmed six species: 2,6-diiodohydroquinone (I_2 -HQ), 3-iodo-4-hydroxybenzoic acid (I-HBA), 3,5-diiodo-4-hydroxybenzoic acid (I_2 -HBA), 3-iodo-4-hydroxyphenylacetic acid (I-HPA), 3,5-diiodo-4-hydroxyphenylacetic acid (I_2 -HPA), and 3-(4-hydroxy-3-iodophenyl)propionic acid (I-HPPA) (Table S5). The other four species were thought to be isomers of I-HBA (retention time of 19.638 min), iodothyroacetic acid (33.260 min), or hydroxylated forms of I-HBA (21.665 and 22.654 min); however, their confirmation was hindered by the lack of authentic standards.

Iodine-Containing Compounds and TH Metabolism.

All confirmed species had detection rates of >96% and were highly correlated with each other [most r values were >0.5, Spearman correlation analysis (Figure S6)]. Notably, all species had similar structures, i.e., with iodine atom(s) on the *ortho* site(s) of the hydroxyl group, whereas a hydroxyl, carboxyl, or carboxylic alkyl group was located at the only *para* position on the phenyl ring. These prevailing substitution patterns strongly implied the presence of a well-organized source.

Considering that the THs are the major iodine-containing compound in the human body, we speculated that the confirmed species were derived from THs. *In vitro* metabolism experiments of T4 with HRP confirmed our hypothesis. Five species (I_2 -HQ, I-HBA, I_2 -HBA, I-HPA, and I_2 -HPA) were detected in the experimental groups, but not in any negative control (Figure S7). Specifically, I_2 -HQ was the exact product of the outer phenyl ring of T4 through ether-link cleavage, whereas the other products were derived from the inner ring, with further deamination and decarboxylation on the side chain. This experiment confirmed the metabolic origins of the detected iodine-containing species.

Environment-Induced TH Metabolic Alteration. Table S6 shows the concentrations of TH metabolites in each phase. In contrast to the lack of changes in the urinary iodine level and bloodstream levels of thyrotropin-releasing hormone (TRHs), T3, or T4, we found that traveling from LA to Beijing significantly decreased the levels of I_2 -HQ [−35.0%, 95% confidence interval (CI) from −52.7% to −10.1%], I-HBA (−32.0%, 95% CI from −48.8% to −8.1%), I_2 -HBA (−45.5%, 95% CI from −59.5% to −27.2%), and I-HPA (−52.4%, 95% CI from −70.5% to −21.2%); there were also marginally significant reductions in the levels of I-HPA and I_2 -HPA in Beijing. As shown in Figure 2, all metabolite reductions were reversed after the participants returned to LA. These findings suggest that environmental changes have a significant impact on urinary levels of TH metabolites, indicating the environmental sensitivity of such metabolic changes.

There was considerable variation in environmental factors between Beijing and LA, including exposure to polycyclic aromatic hydrocarbons (PAHs), second-hand smoke (cotinine), and bisphenol A (BPA), as previously reported.^{15,17,18} In the study presented here, we also found significant increases in the levels of strontium (Sr), nickel (Ni), tin (Sn), barium (Ba), and lead (Pb) in Beijing, along with decreases in the levels of lithium (Li), chromium (Cr), manganese (Mn), cadmium (Cd), antimony (Sb), and bromine (Br) (Table S6). To identify key factors, we performed mediation analyses that explored the extent to which a single exposure could explain the between-city difference in TH metabolites. We found that exposures to PAHs, including 2-hydroxydibenzofuran (2-OHDBF) and 2/3-hydroxyfluorenes (OHFLUs), and elements such as Br, Li, Sb, Mn, and Cd statistically explained the changes in TH metabolite concentrations during the travel. The other environmental factors (cotinine, Ni, Pb, Sr, and Sn) were also strongly associated with TH metabolite levels, but this relationship indicated a negative influence [i.e., opposite direction from that of 2-OHDBF/OHFLUs (Figure S8)]. These results are consistent with previous studies.^{21,22}

Oxidative stress is a general pollutant-associated physiological response. Previously, we found associations between 2-OHDBF/OHFLUs and oxidative biomarkers, such as urinary MDA and 8-isoprostane, in the same cohort.¹⁷ Here, we found that exposure to Br, Li, Mn, Sb, and Cd was also associated with oxidative changes (Figure S9a). Consistent with the ether-link cleavage of THs by attack from reactive oxygen species (ROS), the primary outer ring metabolite of T4 (i.e., I_2 -HQ) had significant positive associations with urinary MDA and 8-isoprostane, but it showed a negative association with uric acid, a crucial antioxidant in the blood (Figure 3). These associations remained robust in sensitivity analysis (Figure

S9b) and were observed among other TH metabolites except for I_2 -HPA.

DISCUSSION

To the best of our knowledge, this is the first study to systematically identify metabolites in urine as feasible and sensitive markers of TH metabolism by developing a unique organoiodine metabolomic approach. We extended a previous method for ambient particles²³ to urine samples, identified 42 iodine-containing compounds, and confirmed the structures of six species. We carefully considered a potential exogenous source, such as I-HBA from iodo-disinfection byproducts in drinking water; however, such an origin was ruled out by the failure to detect other typical byproducts (i.e., iodoacetic acid, 2,4,6-triiodophenol, or 4/5-iodosalicylic acids).^{24–26} Structural characteristics similar to those of THs indicated their endogenous source; they were verified as TH metabolites through *in vitro* experiments.

We leverage data from a comprehensive biomarker-based exposure assessment to identify potential environmental thyroid hormone-disrupting chemicals. Changes in most TH metabolites were associated with exposure biomarkers of PAHs and metals, which can likely be attributed to their pro-oxidative effects. ROS have been previously shown to trigger the ether-link cleavage of T4, a process that can be hindered by antioxidants.^{27,28} Consistently, we found that changes of I_2 -HQ were positively associated with the oxidative markers of urinary 8-isoprostane and MDA, while they were negatively associated with the antioxidative marker of uric acid. Furthermore, these oxidative and antioxidant compounds were also associated with exposure to PAHs and metals, which mechanistically supports the associations between TH metabolites and exposure to PAHs and/or metals.

Our results proposed novel mechanistic insights concerning the association of THs with exposure to environmental pollutants.²⁹ Considering that the cleavage of a diphenyl ether link is an irreversible clearance pathway for THs, its blockage could lead to the accumulation of THs in the bloodstream. Accordingly, we observed numerically increased TH levels in women after they had traveled from LA to Beijing, which were accompanied by no significant changes in serum TRH or urinary iodine levels (Figure S10). These results suggest that the inhibition of peripheral metabolism, compared with the classic HPT axis, is more likely to drive the slightly increased TH levels in response to pollutants. Importantly, the urinary TH metabolites appear to be more sensitive to environmental changes, compared with circulating levels, and therefore may be promising biomarkers for identifying environmental thyroid-disrupting chemicals in human studies.

This study has several limitations. First, we utilized a natural experiment but were restricted by the limited participant pool. Second, although we achieved a high-exposure scenario of 10 weeks through the international travel design, this duration was insufficient for substantial perturbation of circulating THs, especially considering their high level of storage in the thyroid gland.⁶ Another limitation is that we cannot address the potential influence of the climate difference between the two cities due to the lack of personal measurements of exposure to temperature and other factors. Therefore, further studies with more participants and longer, more refined exposure are warranted to evaluate the impacts and subsequent health effects of such environmentally sensitive peripheral TH

metabolism, and more animal studies are also needed to help understand the potential mechanisms.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.estlett.4c00428>.

Synthesis and identification of iodine-containing compounds; *in vitro* metabolism experiments; measurement of serum thyroid hormones; measurement of urinary elements; sensitivity analysis; reference standards and reagents for synthesis (Table S1); quality assurance (QA), quality control (QC), and multiple-reaction monitoring parameters used for serum thyroid hormone detection (Table S2); information about 42 iodine-containing compounds (Table S3); detailed information about 10 iodine-containing compounds with known molecular formulas (Table S4); QA and QC for confirmed iodine-containing compounds (Table S5); concentrations of serum metabolites and urinary metabolites (Table S6); structures of reference standards in both original and methylated forms (Figure S1); ^1H and ^{13}C NMR spectra of I-HPPA, I-HPA, and I₂-HPA (Figures S2–S4); EI chromatogram of synthesized I₂-HQ (Figure S5); Spearman correlations of iodine-containing compounds (Figure S6); extracted ion chromatograms of the *in vitro* experiment (Figure S7); contribution of individual exposure (Figure S8); associations between exposure and urinary oxidative biomarkers along with sensitivity analysis of urinary oxidative biomarkers and TH metabolites (Figure S9); and concentrations of markers in three phases (Figure S10) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Yan Lin – Department of Environmental Health Sciences, Jonathan and Karin Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California 90095, United States; Nicholas School of the Environment and Global Health Institute, Duke University, Durham, North Carolina 27708, United States; Email: yan.lin@duke.edu

Yifang Zhu – Department of Environmental Health Sciences, Jonathan and Karin Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California 90095, United States; orcid.org/0000-0002-0591-3322; Email: yifang@ucla.edu

Xinghua Qiu – SKL-ESPC and SEPKL-AERM, College of Environmental Sciences and Engineering, and Center for Environment and Health, Peking University, Beijing 100871, P. R. China; orcid.org/0000-0001-9874-8030; Email: xhqiu@pku.edu.cn

Authors

Qianqian Chai – SKL-ESPC and SEPKL-AERM, College of Environmental Sciences and Engineering, and Center for Environment and Health, Peking University, Beijing 100871, P. R. China

Jinming Liu – SKL-ESPC and SEPKL-AERM, College of Environmental Sciences and Engineering, and Center for

Environment and Health, Peking University, Beijing 100871, P. R. China

Xiaodi Shi – SKL-ESPC and SEPKL-AERM, College of Environmental Sciences and Engineering, and Center for Environment and Health, Peking University, Beijing 100871, P. R. China; orcid.org/0009-0008-4062-4009

Xing Jiang – SKL-ESPC and SEPKL-AERM, College of Environmental Sciences and Engineering, and Center for Environment and Health, Peking University, Beijing 100871, P. R. China

Xinchen Lu – SKL-ESPC and SEPKL-AERM, College of Environmental Sciences and Engineering, and Center for Environment and Health, Peking University, Beijing 100871, P. R. China

Lailai Yan – Department of Laboratorial Science and Technology, School of Public Health, Peking University, Beijing 100191, P. R. China

Junfeng Zhang – Nicholas School of the Environment and Global Health Institute, Duke University, Durham, North Carolina 27708, United States; orcid.org/0000-0003-3759-6672

Tong Zhu – SKL-ESPC and SEPKL-AERM, College of Environmental Sciences and Engineering, and Center for Environment and Health, Peking University, Beijing 100871, P. R. China; orcid.org/0000-0002-2752-7924

Jesus A. Araujo – Department of Environmental Health Sciences, Jonathan and Karin Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California 90095, United States; Division of Cardiology, Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, California 90095, United States

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acs.estlett.4c00428>

Notes

The authors declare no competing financial interest.

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